

REMARKS

Following entry of this amendment, claims 1, 6-17, 19, and 24-29 will be pending in this application. Claims 2-5, 18, and 20-23 are canceled herein; claims 1, 16, 19, and 24 are currently amended; and new claims 25-29 are added. Claims 6-15 were withdrawn from consideration based on an earlier restriction. New claims 25-29 are directed to oligonucleotides and kits comprising oligonucleotides, and should therefore be considered with the claims currently under examination. Support for the amendments and new claims can be found throughout the specification and claims as filed, e.g., at page 5, lines 2-4; page 9, lines 28-33; and page 16, lines 10-13.

35 USC § 102

Claims 1, 2, 4, and 5 were rejected as allegedly anticipated by Luo et al., 2002, Biochem. Genet., 40:41-51 ("Luo").¹ Applicants respectfully disagree, but have amended the claims solely to further prosecution and obtain allowable subject matter. Claims 2, 4, and 5 are canceled herein without prejudice, thereby obviating the rejection with regard to those claims.² To the extent that the rejection may be applied to claim 1 as presently amended, applicants respectfully traverse. To anticipate a claim, a reference must teach every element of the claim. Although Luo discloses nucleic acids that comprise SEQ ID NO:1 (see Fig. 4), Luo neither teaches nor suggests an oligonucleotide having a sequence consisting of SEQ ID NO:1, as recited in amended claim 1. Therefore, claim 1 is novel over Luo, and applicants request reconsideration and withdrawal of the rejection.

¹ Claims 1, 2, 4, and 5 were rejected as allegedly anticipated by Luo under 35 USC § 102(b). However, Luo is not available as prior art under section 102(b). This application was filed under 35 USC § 371 from an international application having a filing date of September 30, 2002. Luo was published in February 2002, less than one year before the effective filing date. Applicants request that the Examiner consider whether Luo is available under section 102(a). GenBank Accession No. AF279907, which includes a sequence disclosed in Luo and which the Office action appears to quote at pages 8-9, was first available on February 14, 2001. See reference AO submitted with the Information Disclosure Statement dated November 22, 2005.

² Canceled claim 5 was rejected over Luo. Applicants note for the record that the alignment presented by the Office at pages 8-9 of the instant application comparing GenBank Accession No. AF279907 and SEQ ID NO:2 contains one mismatch at the position corresponding to nucleotide 41 of SEQ ID NO:2. Therefore, Luo would not anticipate a claim to a nucleotide comprising or consisting of SEQ ID NO:2.

Claims 1-3 were rejected under 35 USC § 102(b) as allegedly anticipated by Marsh et al., 1999, Genomics, 58:310-312 ("Marsh"). Applicants respectfully disagree, but have amended the claims solely to further prosecution and obtain allowable subject matter. Claims 2 and 3 are canceled herein without prejudice, thereby obviating the rejection with regard to those claims. To the extent the rejection may be applied to claim 1 as presently amended, applicants respectfully traverse. To anticipate a claim, a reference must teach every element of the claim. Marsh does not disclose within its "four corners" the nucleic acid sequences alleged by the Office, although Marsh does refer to GenBank Accession No. AF127519,³ which the Office action appears to quote at page 11. Although GenBank Accession No. AF127519 discloses a nucleic acid that comprises SEQ ID NO:1, it neither teaches nor suggests an oligonucleotide having a sequence consisting of SEQ ID NO:1, as recited in claim 1 as amended. Therefore, claim 1 as amended is novel over both Marsh and GenBank Accession No. AF127519, and applicants request reconsideration and withdrawal of the rejection.

35 USC § 103

Claims 16 and 18 were rejected as allegedly unpatentable over Marsh in view of Luo and Stratagene 1988 catalog ("Stratagene"). Claim 18 is canceled herein, thereby obviating the rejection with regard to that claim. To the extent that the rejection may be applied to claim 16 as presently amended, applicants respectfully traverse on the grounds that a *prima facie* case of obviousness has not been made. None of Marsh, Luo, or Stratagene teaches or suggests an oligonucleotide consisting of the nucleotide sequence of SEQ NO:1 or the exact complementary sequence thereof, an oligonucleotide consisting of SEQ ID NO:2 or the exact complementary sequence thereof, or the provision of the oligonucleotides in a kit for identifying the number of tandem repeats in the promoter region of a human thymidylate synthase (TS) gene. As discussed above, Marsh does not disclose within its "four corners" any nucleic acids comprising or consisting of SEQ ID NO:1 or its complement. Similarly, Marsh does not disclose any nucleic acids comprising or consisting of SEQ ID NO:2 or its exact complement. Luo and Stratagene

³ A copy of GenBank Accession No. AF127519 was previously submitted to the Office in the Information Disclosure Statement submitted November 22, 2005. This listing was first available on July 15, 1999.

fail to remedy the deficiencies of Marsh. Stratagene does not disclose any nucleic acid sequences, and Luo does not teach or suggest nucleic acids comprising or consisting of SEQ ID NO:2 or its exact complement. As can be seen in the alignment presented on page 13 of the Action, there is one mismatch between SEQ ID NO:2 and the sequence presented by the Office as being derived from Luo. That mismatch is at the position corresponding to nucleotide 41 of SEQ ID NO:2. Further, the Office has not alleged, and the references do not provide, any specific rationale for selecting the specific oligonucleotides consisting of SEQ ID NO:1 and SEQ ID NO:2 (or their complements) for incorporation in a kit. One of ordinary skill in the art would not have been motivated to modify the teachings of any of Marsh, Luo, and Stratagene to arrive at the kits recited in claim 16. Applicants therefore request reconsideration and withdrawal of the rejection.

Claims 17 and 19 were rejected as allegedly unpatentable over Marsh in view of Luo and Stratagene, as applied to claim 16, and further in view of Dobrowolski et al., US 2004/0219557 (“Dobrowolski”). Applicants respectfully traverse, incorporating the arguments above that no *prima facie* case of obviousness has been made with regard to claim 16, but it is worth repeating that Marsh does not disclose nucleic acids comprising or consisting of SEQ ID NO:1 or SEQ ID NO:2 or their exact complements, and Luo and Stratagene do not remedy this deficiency.

Additionally, the Office action (at page 16) states:

As noted in *In re Aller*, 105 USPQ 233 at 235, More particularly, where the general conditions of a claim are disclosed in the prior art (Luo et al. and Marsh et al.), it is not inventive to discover the optimum or workable ranges by routine experimentation.’ Routine optimization is not considered inventive and no evidence has been presented that the selection of oligonucleotide length or hybridization conditions performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Applicants submit that *In re Aller* is inapposite here. The claims at issue in *In re Aller* were directed to processes for the production of phenol. 105 USPQ 233, 234 (C.C.P.A. 1955). The prior art disclosed an identical method, except with conditions of higher temperatures and lower concentrations of one reagent than the claimed invention. *Ibid.* The claims at issue in this

application are directed to compositions, not processes, and as such do not have anything that could be characterized as “general conditions.” Even if Marsh, Luo, and Stratagene did disclose nucleic acids comprising SEQ ID NO:1 and SEQ ID NO:2, the Office action articulates no reasoning how or why one would optimize the “general conditions” of such sequences to arrive at the claimed kits. Although Marsh and Luo disclose that polymorphisms of the TS promoter exist, the only means for detection disclosed are PCR-length analysis and sequencing. No teaching or suggestion is made to determine promoter polymorphism status by means of hybridization analysis, which is the rationale for using the particular oligonucleotides specified in the claims.

Dobrowolski is presented by the Office as providing the general concepts of labeling of oligonucleotides with detectable labels, e.g., FITC and RED640, and detection of polymorphisms using hybridization probes. However, the methods of Dobrowolski would not be directly applicable to analyzing TS promoter polymorphisms. All of the polymorphisms described in Dobrowolski (i.e., single nucleotide substitutions and a deletion of seven nucleotides with a concomitant insertion of three nucleotides at the same position) are substantially different from the TS promoter polymorphisms (i.e. differences in the number of tandem repeats in the promoter region). The Dobrowolski methods rely on differential hybridization of the probes or primers to sequences that differ from each other in at least one nucleotide.⁴ In contrast, the TS promoter polymorphisms do not have different or unique sequences, but rather a change in the number of identical 28-bp repeats. The oligonucleotides of the claimed kits detect differences in the number of repeats by virtue of the SEQ ID NO:1 oligonucleotide’s hybridizing differentially between the perfect repeats and a downstream imperfect repeat. This can be observed in Figure 1 of the instant application. When the oligonucleotides hybridize to the 3R-type promoter, SEQ ID NO:1 makes a perfect Watson-Crick match with the promoter sequence. However, when the oligonucleotides hybridize to the 2R-type promoter, SEQ ID NO:1 hybridizes with five out of eight nucleotides mismatched at the 3' end of the SEQ ID NO:1 oligonucleotide. Because of the mismatches, SEQ ID NO:1 can hybridize to the 3R-type promoter under more stringent

⁴ I.e., the polymorphisms create unique sequences that are not found in the wild-type form of the gene encoding the biotinidase enzyme.

conditions than it can hybridize to the 2R-type promoter, allowing for identification of the number of tandem repeats. Such a method is neither taught nor suggested by Marsh, Luo, Stratagene, or Dobrowolski, nor any combination thereof. Therefore, the claims are unobvious over the combination, and applicants request reconsideration and withdrawal of the rejection.

Claims 20-22 were rejected as allegedly unpatentable over Luo in view of Wittwer et al., U.S. Pat. 6,174,670. Claims 20-22 are canceled herein without prejudice, thereby obviating the rejection.

Claim 23 was rejected as allegedly unpatentable over Marsh in view of Dobrowolski. Applicants respectfully traverse. The Office alleges (at page 21) that Marsh “teaches an oligonucleotide consisting of SEQ ID NO: 1.” This is simply not the case. As discussed above, Marsh does not disclose within its “four corners” any nucleic acids comprising or consisting of SEQ ID NO:1. Even if Marsh could be said to disclose a nucleic acid comprising SEQ ID NO:1 by virtue of its mention of GenBank Accession No. AF127519, such a disclosure is not the equivalent of disclosing an oligonucleotide consisting of SEQ ID NO:1. The Office action states (at page 21) that it would have been obvious in view of Marsh to make or synthesize an oligonucleotide consisting of SEQ ID NO:1, because “where the general conditions of a claim are disclosed in the prior art (Marsh et al.), it is not inventive to discover the optimum or workable ranges by routine experimentation,” again citing *In re Aller*. As discussed above, a disclosure of a long sequence that happens to contain the presently claimed short sequence is not the equivalent of a disclosure of “general conditions” that can be “optimized,” and the claim does not recite any “optimum or workable ranges.” The claim recites a composition. Even if Marsh could be said to have disclosed the sequences alleged by the Office, all this would provide would be at most the equivalent of a disclosure of a large genus of shorter nucleic acids of varying lengths. The Office has articulated no reasoning why one of ordinary skill in the art would select the specific length and sequence claimed. SEQ ID NO:1, in fact, has the particularly useful property of being usable to distinguish between the 2R and 3R forms of the TS promoter by hybridization methods. As discussed above, unlike the polymorphisms disclosed in Dobrowolski, the TS promoter polymorphisms do not have any unique sequences, but rather a change in the number of identical 28-bp repeats. Therefore, the methods of Dobrowolski are not

directly applicable to analysis of the TS promoter. Presented with the combination of Marsh and Dobrowolski, one of ordinary skill in the art would not have been motivated to select SEQ ID NO:1 for any purpose. Therefore, claim 23 is unobvious over the combination of Marsh and Dobrowolski, and applicants request reconsideration and withdrawal of the rejection.

Claim 24 was rejected as allegedly unpatentable over Luo in view of Dobrowolski. As discussed above, Luo does not teach or suggest nucleic acids comprising or consisting of SEQ ID NO:2. As can be seen in the alignment presented on page 24 of the Action, there is one mismatch between SEQ ID NO:2 and the sequence presented by the Office as being derived from Luo. That mismatch is at the position corresponding to nucleotide 41 of SEQ ID NO:2. The Office action states that it would have been obvious in view of Luo to make or synthesize an oligonucleotide consisting of SEQ ID NO:2, because “where the general conditions of a claim are disclosed in the prior art (Marsh et al.), it is not inventive to discover the optimum or workable ranges by routine experimentation,” citing *In re Aller*. As discussed above, Luo does not disclose “general conditions” that have anything to do with the presently claimed composition, and the claim does not recite any “optimum or workable ranges.” The claim recites a composition. All Luo provides by its disclosure of the 165-bp sequence presented by the Office is the equivalent of a disclosure of a large genus of shorter nucleic acids of varying lengths. The Office has articulated no reasoning why one of ordinary skill in the art would select from Luo’s 165-bp sequence the specific length and sequence claimed, including altering the nucleotide corresponding to position 41 of SEQ ID NO:2. The oligonucleotide of SEQ ID NO:2, in fact, has the particularly useful property of being usable to distinguish between the 2R and 3R forms of the TS promoter by hybridization methods. As discussed above, unlike the polymorphisms disclosed in Dobrowolski, the TS promoter polymorphisms do not have any unique sequences, but rather a change in the number of identical 28-bp repeats. Therefore, the methods of Dobrowolski are not directly applicable to analysis of the TS promoter. Presented with the combination of Luo and Dobrowolski, one of ordinary skill in the art would not have been motivated to select SEQ ID NO:2 for any purpose. Therefore, claim 24 is unobvious over the combination of Luo and Dobrowolski, and applicants request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. Upon a finding that claim 1 is allowable, applicants request rejoinder of withdrawn claims 6-15, all of which depend directly or indirectly from claim 1.

This reply is being submitted with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 18201-0003US1.

Respectfully submitted,

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